IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
David RING

For: METHOD OF PROMOTING AN IMMUNE RESPONSE WITH A BISPECIFIC ANTIBODY

Serial No.: 08/349,489

Filed: December 2, 1994

Atty.Dkt No.: PP00999.104 (CHIR-999/00US)

Examiner: A. Holleran

Group Art Unit: 1642

Confirmation No.: 6479

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF JUSTIN G. P. WONG, Ph.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Justin G. P. Wong, hereby declare as follows:

1. I received my Ph.D. in Immunology from Harvard University in 1992. I am currently a Principle Scientist at Chiron Corporation in Emeryville, CA and have been at Chiron since 2000. Before joining Chiron, I was a Scientist at Strata Biosciences in Alameda, CA. A copy of my Curriculum Vitae (Exhibit A) is attached hereto.

2. I am extremely familiar with studies of both antibodies having actively studied, worked and published in this discipline for over 19 years. I have co-authored numerous publications and patents in the field of antibodies.

3. I have reviewed pending Patent Application Serial No. 08/349,489 for "METHOD OF PROMOTING AN IMMUNE RESPONSE WITH A BISPECIFIC ANTIBODY" by Ring (hereinafter "the specification") and the currently pending claims. I have also reviewed the Office Action dated December 18, 2002 and the references cited therein including Rudikoff (1982) *Proc. Nat'l Acad. Sci. USA* 79:1979 (hereinafter "Rudikoff"); PCT GB/90/02017 (hereinafter "Adair"); Panka et al. (1988) *Proc. Nat'l Acad. Sci. USA* 85:3080-3084 (hereinafter "Panka"); Hsieh-Ma et al. (1992) *Cancer Research* 52:6832-6839 (hereinafter "Hseih-Ma"); Weiner et al. (1993) *Cancer Research* 53:94-100 (hereinafter "Weiner"); Ring et al. in "Breast Epithelial Antigens" ed. R.L. Ceriani, pp. 99-104 (1991) (hereinafter "Ring"); Fanger (1992) *Critical Reviews in Immunology* 12(3,4):101-124 (hereinafter "Fanger"); and

Snider et al. (1990) *J. Exp. Med.* 171:1957-1963 (hereinafter "Snider"). Therefore, I am familiar with the issues raised by the Examiner in the Office Action.

4. I understand that the pending claims are directed to methods of inducing production of antibodies against a cancer antigen by administering a bispecific antibody capable of recognizing and binding both FcγRIII and a specified cancer antigen.

5. It is my opinion that, as a technical matter, a skilled worker could have readily practiced the methods of the pending claims in light of the specification, together with the common general knowledge, tools and methods available as of the effective filing date of January 1994. It is further my opinion that the references cited by the Examiner do not teach or suggest the methods as set forth in the claims. I base these opinions on the facts set forth below; however, I call attention to the fact that using bispecific antibodies which binds both FcγRIII and one of the cancer antigens set forth in claim 1 would not have required undue experimentation and that the induction of antibodies against the cancer antigen was not suggested by the references. In drawing my conclusions, I have considered the nature of the claims, the quantity of experimentation required to practice the subject matter of the claims, the direction present in the specification, the state of the field at the time the application was filed, the teachings of the cited references and the level of skill in the art.

6. At the outset, I note that the term "skilled worker" with a routine level of skill in the field of molecular biology in December 1994 had a Ph.D. degree and two or more years of post-doctoral training.

7. In December 1994, the quantity of experimentation required to make bispecific antibodies that recognized FcγRIII and a cancer antigen was quite low. At the time of filing and as described in the specification, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. (*See,* for example, page 10, lines 6-16). One working in this field could have readily selected suitable cancer antigens, for example as described in detail on pages 17-20. Also well known at the time of filing were techniques of producing bispecific antibodies and these standard procedures are described throughout the specification as filed, for example, on page 9, line 12-28 (including the references cited therein). Based on these extensive teachings regarding each of the antigens recognized by the claimed bispecific antibody and, additionally, the extensive teachings regarding production of bispecific antibodies, it is evident that a skilled worker would have easily produced bispecific antibodies which bound both FcγRIII and a cancer antigen. Thus, it is clear from the specification that 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. Therefore, it is my opinion that it would have required only routine experimentation for the skilled worker to make a bispecific antibody that recognized FcγRIII and a cancer antigen, as recited in the pending claims.

8. Furthermore, the specification provides working examples and additional significant direction for evaluating whether a FcγRIII-cancer antigen binding bispecific antibody could be used to elicit an antibody response to the cancer antigen. Those of us working in the field of bispecific antibodies are well versed in administration of antibodies and in the various tests for determining whether antibodies are elicited, for example using assays described on pages 24-29 of the specification. Examples present in the specification demonstrate such assays. (See, Examples 2 and 3). Furthermore, since preparing bispecific antibodies in December of 1994 was well within the purview of a skilled worker, even if a particular bispecific antibody were inoperable for some reason (*e.g.*, it did not elicit antibodies against the cancer antigen), the skilled worker would have readily used the molecule as a starting point in order to design bispecific antibodies with the desired characteristics.

9. It is further my opinion that Rudikoff, Adair or Panka do not accurately reflect the state of research in the field of bispecific antibodies as of December 1994. I base this opinion on the following facts. First, these references do not in any fashion address bispecific antibodies as used in the claimed methods. Rudikoff and Panka address how single amino acid substitutions in the CDR of an antibody can alter binding. Adair is directed to humanized antibody molecules (HAMs) having specificity for carcinoembryonic antigen (CEA) and to processes for their production using recombinant DNA technology. (See, Abstract). Nothing in these references is relevant to the claimed methods. Further, as all these references were published at least 3 years prior to December 1994, they are not representative of the state of the art at the time of filing.

10. Thus, it is my opinion that a skilled worker could have readily designed, made, tested and used a bispecific antibody falling within the scope of the claims. As noted above, bispecific antibodies were routinely made and administered. Similarly, assays for testing antibody production were routine in December 1994. The generation and testing of bispecific antibodies is described in Fanger et al. (1991) *Trends Biotechnol* 9(11):375-80 (Exhibit B) and Ring et al. "Breast Epithelial Antigens: Molecular Biology to Clinical Applications" (Exhibit C), as well as U.S. Patent Nos. 4,714,681 and 4,474,893 (Exhibit D). These and other references address the pertinent question at issue here -- whether bispecific antibodies that recognize FcγRIII and a cancer antigen can be made and used to produce antibodies against the cancer antigens following the teachings of the specification. These references plainly confirm that neither making bispecific antibodies nor testing antibody production in response to administration of these antibodies were unpredictable as of December 1994. Further, they are clearly representative of the high level of existing skill in the art and the fact that generation of bispecific antibodies was considered routine and entirely predictable in December 1994. In sum, to the skilled worker, making and using the claimed bispecific antibodies would have been routine and would have required little or no experimentation, particularly in light of the clear

guidance in the specification regarding how to make, test and use bispecific antibodies as claimed.

11. In view of the foregoing facts regarding the routine nature of experimentation required to make, use and deliver bispecific antibodies directed against FcγRIII and a cancer antigen, the extensive direction provided by the specification, the straightforward nature of the claimed subject matter, the high level of the skilled worker, the sophistication of the art, and the predictability of the art, it is my unequivocal opinion that the specification enabled, in December 1994, a skilled worker to practice the methods as claimed.

12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. The fact that bispecific antibodies can have induce such antibodies was, in fact, a surprising finding made by the present inventors *after* all of the references were published, as noted on page 6, lines 24-28 of the specification:

> It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen.

Nowhere do any of the references report or test antibody production in response t4 the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Date Justin G. P. Wong, Ph.D.